REMARKS

Claims 40 and 54-101 are pending in the present application. Claims 58, 59, 61, 62, 69, 70, 72, 73, 79, 80, 82-84, 90, 91, 93, 94, and 99-101 are amended herein. Claims 55-57, 66-68, 76-78, and 87-89 are canceled herein without prejudice to prosecution at a later date. Claims 69, 70, 90, and 91 have been amended to correct improper multiple dependencies. No new matter has been introduced by way of this amendment.

Preliminarily, Applicants have submitted herewith fourteen pages of formal drawings to the Drawing Review Branch in accordance with 37 C.F.R. § 1.84. Entry of the formal drawings is respectfully requested.

I. The claims are definite in accordance with 35 U.S.C. § 112, second paragraph.

Clarification of the meaning of the phrase "substantially no toxicity" or "substantially reduced toxicity" has been requested by the Examiner. Applicants submit that these phrases mean that the *H. pylori* cytotoxin polypeptides do not exhibit statistically significant cytotoxic effects to a *Helicobacter pylori* host. "Cytotoxic" means the ability to cause cell vacuolation and cell death. As humans are a *H. pylori* host, the cytotoxin polypeptides of the invention have substantially no toxicity or substantially reduced toxicity in humans. As explained in the specification, the polypeptides of the invention may be used in vaccine and diagnostic applications. (Specification at page 4, lines 1-8.) Each of the polypeptides of the invention may be used as a sole vaccine candidate. (Specification at page 38, lines 32-35.) Accordingly, the cytotoxin polypeptides of the invention *may* be acceptable for use in human vaccines, though this should not be interpreted as a limitation of the claimed polypeptides.

Claims 55, 58, 59, 76, 79, and 80 are rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite in the recitation of "fragments of the *H. pylori* CT polypeptide further comprising fragments of the *H. pylori* CT polypeptide." Applicants traverse. Nonetheless, to advance prosecution of the application, claims 55, and 76 have been canceled without prejudice. Claims 58, 59, 79, and 80 have been amended to omit the language at issue. Accordingly, Applicants submit that the amended

claims clearly define the metes and bounds of the invention and request withdrawal of the rejection.

Claims 55, 57-59, 76, and 78-80 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite in the recitation of the term "derivatives." Applicants traverse. While claim limitations must be supported in the specification through express, implicit, or inherent disclosure, there is no *in haec verba* requirement. MPEP § 2163 I.B. Applicants submit that the term "derivatives" is implicitly defined in the specification. For example, the term "polypeptide" as defined in the specification includes polypeptides having post-translational modifications, such as glycosylations, acetylations, and phosphorylations, polypeptides containing one or more amino acid analogs, and polypeptides having substituted linkages. (Specification at page 14, lines 8-20). "Derivatives" further includes polypeptides containing amino acid substitutions and deletions that do not substantially affect the function of the polypeptide as compared to a reference polypeptide. (Specification at page 7, lines 13-37.) Accordingly, Applicants submit that the term "derivatives" sufficiently conveys the metes and bounds of the invention. Nonetheless, to advance the prosecution of the case, claims 55, 57, 76, and 78 have been canceled without prejudice. Claims 58, 59, 79, and 80 have been amended to omit the language at issue. Applicants request reconsideration and withdrawal of the rejection.

Claims 58 and 79 also are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite in the recitation of the phrase "immunologically identifiable with." Applicants traverse. The phrase "immunologically identifiable with" is used in the specification at page 14, lines 21-30 and describes a polypeptide of the invention that is recognized by or is able to react with at least one antibody raised to an epitope of the reference polypeptide, for example, the polypeptide of SEQ ID NO:3. Accordingly, Applicants submit that the phrase is sufficiently clear to convey the metes and bounds of the invention and request withdrawal of the rejection.

Claims 59 and 80 have been rejected as allegedly indefinite in the recitation of the phrase "said polypeptide." Applicants traverse the rejection. Nonetheless, to advance prosecution of the application, claims 59 and 80 have been amended to clarify that the phrase "said polypeptide" refers to the recited CT

polypeptide. Additionally, the term "the" has been removed to provide clear antecedent basis for the term "functional aspects." As explained in the specification, "functional aspects" refer, for example, to the biological activity of the polypeptide. (Specification at page 7, lines 30-37.) The phrase "which do not substantially affect the functional aspects" means, for example, that a given alteration does not substantially change the biological activity of the polypeptide. (Specification at page 7, lines 30-37.) Applicants submit that claims 59 and 80 are sufficiently clear to convey the metes and bounds of the invention and request withdrawal of the rejection.

Applicants request clarification of the rejection of the term "immunogenic" in claim 74. "Immunogenic" as recited in claim 74 is defined in the Specification as the ability of a polypeptide to cause a humoral and/or cellular immune response. For example, an immunogenic polypeptide has at least one epitope from a reference polypeptide. Accordingly, Applicants agree that the recombinant polypeptides recited in claim 74 have at least one epitope from the polypeptide of SEQ ID NO:3.

Claim 84 has been rejected for being allegedly indefinite for failure to recite any functional limitation or the structural limitation that the 15 contiguous nucleotides represent 5 in-frame codons. Applicants traverse. Claim 84 recites an immunogenic, recombinant polypeptide expressed from at least 15 contiguous nucleotides of SEQ ID NO:2, wherein the polypeptide exhibits substantially no toxicity or substantially reduced toxicity. Claim 84 recites both functional and structural limitations of the claimed polypeptide such that the claim is sufficiently clear to one having ordinary skill in the art to convey the metes and bounds of the invention. Nonetheless, to advance prosecution of the application, claim 84 has been amended to recite a polypeptide comprising at least 5 amino acids expressed from at least 15 contiguous nucleotides of SEQ ID NO:2. Accordingly, Applicants request withdrawal of the invention.

II. **The claims are enabled by the specification in accordance with 35 U.S.C. § 112, first paragraph.**

Claims 55, 57-59, 61, 62, 76, 78-80, 82-86, 95, and 96 are rejected for alleged lack of enablement. Applicants traverse. Preliminarily, Applicants note that claims 55, 57, 76, and 78 have been canceled without prejudice.

The enablement requirement of 35 U.S.C. § 112, first paragraph, mandates that the specification teach those in the art how to make and use the claimed invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). The test of enablement is not whether any experimentation is necessary but, whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Wands*, 8 U.S.P.Q.2d at 1404.

The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and
viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of nonenablement ***must*** be based on the evidence as a whole. *Id.* In order to make a rejection, the examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The burden then shifts to the applicant to provide persuasive arguments, supported by suitable proofs where necessary, that one

skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973).

The Examiner asserts that, while the specification is enabling for *H. pylori* cytotoxin of SEQ ID NO:3 or the polypeptide encoded by the polynucleotide of SEQ ID NO:2, and immunogenic fragments thereof, it is not enabling for any polypeptide encoded by any 15 contiguous nucleotides of SEQ ID NO:2, or any derivative of any of the recited polypeptides, having substantially no toxicity.

Applicants submit, however, that the claims do not recite "any" polypeptide encoded by any 15 contiguous nucleotides of SEQ ID NO:2 or "any" derivative of any of the recited polypeptides. The claims recite both functional and structural limitations. For example, claims 58, 59, 61, and 62 recite polypeptides that can induce the production of antibodies to a *Helicobacter pylori* cytotoxin. Claims 79, 80, 82, and 83 recite immunogenic polypeptides comprising at least 10 or at least 15 contiguous amino acids of SEQ ID NO:3. Claims 84-86 as amended herein recite immunogenic polypeptides comprising at least five amino acids expressed from at least fifteen contiguous nucleotides of SEQ ID NO:2. Claims 95 and 96 recite recombinant polypeptides of *Helicobacter pylori* cytotoxin, wherein the cytotoxin causes the vacuolation of eukaryotic cells and the recombinant polypeptide can induce the production of antibodies to a *Helicobacter pylori* cytotoxin. The polypeptides of claims 58, 59, 61, 62, 79, 80, 82-86, 95, and 96 exhibit substantially no toxicity or substantially reduced toxicity. Accordingly, the claims at issue do recite the properties retained in the derivatives, including immunogenicity and reduced or no toxicity. As explained in the Del Giudice declaration submitted August 22, 2000, no undue experimentation would have been required to determine which polypeptides have these properties. (Del Giudice declaration, paragraphs 8-19.)

Additionally, the structure of each of the claimed polypeptides is recited – i.e., the polypeptides of claims 58, 59, 61, 62, 79, 80, and 82-83 are derived from SEQ ID NO:3. The polypeptide of claims 84-86 are derived from the polypeptide expressed by the polynucleotide of SEQ ID NO:2. The polypeptide of claims 95 and 96 are derived from *Helicobacter pylori*. Since the claimed polypeptides are recombinantly produced, they may be generated in and isolated from a variety of expression systems, including

mammalian, insect, bacterial, and yeast systems. (Specification at page 18, line 2 to page 38, line 29.) The techniques for polypeptide expression in and isolation from these systems are well known to those skilled in the art. (*See, e.g.,* Specification at page 26, lines 22-38.) Additionally, expression and purification of the CT polypeptide are demonstrated in Examples i(1)(e) and i(2). As further explained in the specification, toxicity of a polypeptide may be determined by measuring the vacuolating activity of the polypeptide. (See, *e.g.*, Specification at page 46, lines 7-29.) Additionally, the immunogenicity or ability to induce antibody production of a sample may be assessed by techniques well known in the art, such as immunoblotting. (See, *e.g.*, Specification at page 46, line 25 to page 46, line 6.) Accordingly, Applicants submit that the specification provides significant guidance regarding the expression and purification of the claimed polypeptides from various sources.

Given the amount of guidance provided in the specification, the scope of the claims, and the sophistication of one of ordinary skill in the art, one having ordinary skill in the art would be able to make and use the invention without undue experimentation using only the application as a guide. Accordingly, claims 55, 57-59, 61, 62, 76, 78-80, 82-86, 95, and 96 are enabled. Applicants request reconsideration and withdrawal of the rejection.

Applicants further submit that claim 74 is enabled. The Examiner asserts that claim 74 is not enabled because it does not require induction of the production of antibodies specific to *H. pylori*. While the specification discloses diagnostic and vaccine applications, claim 74 is directed to a polypeptide, not a method. The Examiner mistakenly requires a diagnostic or other use of the polypeptide in order for the claim to be enabled. This, however, is not the standard for enablement. The application need only teach how to make and use the invention without undue experimentation. Claim 74 recites an immunogenic polypeptide derived from SEQ ID NO:3. The ability of the polypeptide to produce antibodies specific to *H. pylori* is not required for enablement of the claim. As previously explained, immunogenicity as recited in claim 74 is defined in the specification as the ability of a polypeptide to cause a humoral and/or cellular immune response. That response need not be specific to *H. pylori*. In the context of claim 74, the claimed polypeptide includes polypeptides having at least one epitope from

the polypeptide of SEQ ID NO:3. The immunogenicity of the claimed polypeptide may be assessed by techniques well known in the art, such as immunoblotting. (See, *e.g.*, Specification at page 46, line 25 to page 46, line 6.) One having ordinary skill in the art would be able to make and use the claimed invention without undue experimentation using only the application as a guide. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

III. **Claims 80, 84, 95, and 96 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.**

Claims 80, 84, 95, and 96 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of written description. Applicants traverse.

The fundamental factual inquiry for the written description requirement is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date, the applicant was in possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The written description requirement may be satisfied by describing distinguishing identifying characteristics sufficient to show the applicant was in possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.* 525 U.S. 55, 68 (1998).

The Examiner suggests reciting SEQ ID NO:3 and the ability to induce the production of antibodies to *H. pylori* cytotoxin in the claims at issue to obviate the rejection. Applicants respectfully submit, however, that claim 80 depends upon claims 74 and 75 which recite polypeptides of SEQ ID NO:3. Similarly, claim 84 recites polypeptides encoded by the polynucleotide of SEQ ID NO:2. Those claims further recite that the polypeptides be immunogenic. Thus, the claimed polypeptides have at least one epitope from the polypeptide of SEQ ID NO:3 or the polypeptide encoded by the polynucleotide of SEQ ID NO:2, respectively. Applicants submit that these identifying characteristics demonstrate to a skilled artisan that Applicants were in possession of the claimed invention at the time of filing. Nonetheless, to advance prosecution of the case, claims 80 and 84 have been amended to recite the ability of the claimed polypeptides to produce antibodies to *Helicobacter pylori*.

Claims 95 and 96 recite recombinant polypeptides of a *Helicobacter pylori* cytotoxin that can induce antibodies to a *Helicobacter pylori* cytotoxin, wherein the cytotoxin has vacuolating activity in eukaryotic cells, and that exhibit substantially no toxicity or substantially reduced toxicity. Thus, claims 95 and 96 recite both structural and functional properties of the claimed polypeptide. Contrary to the Examiner's assertion that "a substantial portion of the claimed genus" must be disclosed to satisfy the written description requirement, section 112, first paragraph requires disclosure of a representative number of species. A single species may be adequate to support a genus. What constitutes a representative number of species is an inverse function of the skill and knowledge in the art. *See* MPEP § 2163 II.A.3 (a)(ii). As stated in the Del Giudice declaration, vacuolation assays can be performed for the routine determination of the toxicity of the polypeptides, fragments, and derivatives of the invention. Additionally, one having ordinary skill in the art could use classical immunological assays to screen for antibody production in response to immunizations with fragments of *H. pylori* cytotoxin protein. In light of the structural and functional properties recited in claims 95 and 96 and the representative examples disclosed in the specification, the skilled artisan would have known Applicants were in possession of the claimed invention at the time of filing. Applicants submit that claims 95 and 96 satisfy the written description requirement.

Accordingly, Applicants request reconsideration and withdrawal of the rejection.

IV. The amended claims are patentable over U.S. Patent 6,054,132 to Cover *et al.*

Claims 40, 54-65, 74-86, and 95-101 have been rejected under 35 U.S.C. § 102(e), or alternatively 35 U.S.C. § 103 in view of Cover et al. Applicants disagree. Preliminarily, Applicants note that claims 55-57 and 76-78 have been canceled without prejudice.

A. *Claims 63-65, 84-86, and 99-101*

The Examiner asserts that Cover et al.'s alleged disclosure of a 24 amino acid fragment reading on positions 34-56 of SEQ ID NO:3, a 14 amino acid fragment

reading on positions 168-180 of SEQ ID NO:3, and an 8 amino acid fragment reading on positions 626-632 of SEQ ID NO:3 cover polypeptides "expressed from at least 15 contiguous nucleotides from SEQ ID NO:3." The Examiner is requested to specifically identify the sequences allegedly disclosed by Cover et al. conforming to the enumerated portions of SEQ ID NO:3. Additionally, it is assumed for purposes of this discussion that the Examiner intended to state "expressed from at least 15 contiguous nucleotides from SEQ ID NO:**2**." Given the degeneracy of the genetic code, however, Cover et al. does not teach or suggest that the polypeptides described therein are expressed from any portion of SEQ ID NO:2. In fact, no polynucleotide sequence is taught or suggested by that reference. Accordingly, Cover et al. does not preclude the patentability of claims 63-65, 84-86, and 99-101.

B. *Claims 40, 54, 58-65, 74, 75, 79-86, and 95-101*

Cover et al. describe the purification and direct sequencing of the amino-terminal 23 amino acids of the 87 kDa vacuolating toxin of *Helicobacter pylori* strain 60190, having toxic activity. Cover et al. does not describe a recombinantly produced *H. pylori* CT polypeptide, or fragment thereof, that exhibits substantially no toxicity or substantially reduced toxicity. Cover et al. does not describe a recombinantly produced *H. pylori* CT polypeptide comprising SEQ ID NO:3 or fragments thereof which polypeptide comprises at least ten or fifteen contiguous amino acids, can induce production of antibodies to *H. pylori*, and exhibits substantially no toxicity, or substantially reduced toxicity.

The Examiner asserts that one skilled in the art would have reasonably expected the polypeptide fragments described by Cover et al. to be inherently non-toxic. That a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic. In relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

> To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities.

In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted). The Examiner seems to assert that, since the polypeptide of Cover et al. shares homology with various ion-transporting ATPases, the polypeptide described therein is not necessarily toxic. That the polypeptide may serve another function, however, has no bearing on the toxicity of the polypeptide. The Examiner further alleges that Cover et al. "teaches that numerous non-toxic epitopes exist in view of the significant differences between toxicity-neutralizing antisera titers versus ELISA antisera titers." Applicants submit that the titers of the two assays cannot be compared. The ELISA antisera titer is defined by Cover et al. as "the reciprocal of the highest dilution that produced an optical density of greater than 0.2" (Cover et al. at column 13, lines 53-55), whereas the neutralization assay titer is defined as "the greatest dilution that induced HeLa cell neutral red uptake greater than 3 SD above that induced by medium alone" (Cover et al. at column 14, Table 3). Additionally, a number of possible reasons can be set forth to explain any significant difference in titer values as determined by the ELISA and neutralization assays. The Examiner has not established that the polypeptides of Cover et al. are necessarily nontoxic. Accordingly, the Examiner has not established the inherency thereof.

The Examiner alternatively asserts that the production of nontoxic fragments of Cover et al.'s polypeptides would have been obvious in view of statements made in the Del Giudice declaration. The Examiner, however, has failed to establish any motivation in Cover et al. to prepare nontoxic polypeptide fragments as required by 35 U.S.C. § 103.

Accordingly, Applicants submit that Cover et al. does not preclude the patentability of the solicited claims. Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at 215-557-5908.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Date: September 16, 2002

Respectfully submitted,

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Attachment

Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the application as follows:

IN THE CLAIMS:
Please cancel claims 55-57, 66-68, 76-78, and 87-89 without disclaimer or prejudice to prosecution at a later date.

Please amend claims 58, 59, 61, 62, 69, 70, 72, 73, 79, 80, 82-84, 90, 91, 93, 94, and 99-101 to read as follows:

58 (Amended). The recombinant polypeptide of claim 40 or 54, wherein said polypeptide [further comprising a *Helicobacter pylori* CT polypeptide, a fragment thereof or a derivative thereof, which] is immunologically identifiable with the protein encoded by the amino acid of SEQ ID NO:3.

59 (Amended). The recombinant polypeptide of claim 40 or 54, wherein said polypeptide [further comprising a *Helicobacter pylori* CT polypeptide, a fragment thereof or a derivative thereof, which] contains one or more amino acid substitutions or deletions which do not substantially affect [the] functional aspects of said CT polypeptide.

61 (Amended). The recombinant polypeptide of claim [55] 40 or 54, said polypeptide comprising at least 87 kDa.

62 (Amended). The recombinant polypeptide of claim [55] 40 or 54, said polypeptide comprising at least 100 kDa.

69 (Amended). The recombinant polypeptide of claim [63-65] 63, 64, or 65, wherein said polypeptide [further comprising a *Helicobacter pylori* CT polypeptide, a fragment thereof or a derivative thereof, which] is immunologically identifiable with the protein encoded by the amino acid of SEQ ID NO:3.

70 (Amended). The recombinant polypeptide of claim [63-65] 63, 64, or 65, wherein said polypeptide [further comprising a *Helicobacter pylori* CT polypeptide, a

fragment thereof, or a derivative thereof, which] contains one or more amino acid substitutions or deletions which do not substantially affect the functional aspects of said polypeptide.

72 (Amended). The recombinant polypeptide of claim [66] 63, 64, or 65, said polypeptide comprising at least 87 kDa.

73 (Amended). The recombinant polypeptide of claim [66] 63, 64, or 65, said polypeptide comprising at least 100 kDa.

79 (Amended). The recombinant polypeptide of claim 74 or 75, wherein said polypeptide [further comprising a *Helicobacter pylori* CT polypeptide, an immunogenic fragment thereof or an immunogenic derivative thereof, which] is immunologically identifiable with the protein encoded by the amino acid sequence of SEQ ID NO:3.

80 (Amended). The recombinant polypeptide of claim 74 or 75, wherein said polypeptide [further comprising a *Helicobacter pylori* CT polypeptide, an immunogenic fragment thereof or an immunogenic derivative thereof which] contains one or more amino acid substitutions or deletions which do not substantially affect [the] functional aspects of said CT polypeptide and wherein said polypeptide can induce the production of antibodies to *Helicobacter pylori*.

82 (Amended). The recombinant polypeptide of claim [76] 74 or 75, said polypeptide comprising at least 87 kDa.

83 (Amended). The recombinant polypeptide of claim [76] 74 or 75, said polypeptide comprising at least 100 kDa.

84 (Amended). An immunogenic, recombinant polypeptide comprising at least 5 amino acids expressed from at least 15 contiguous nucleotides of SEQ ID NO:2, wherein

said polypeptide exhibits substantially no toxicity or substantially reduced toxicity and wherein said polypeptide can induce the production of antibodies to *Helicobacter pylori*.

90 (Amended). The recombinant polypeptide of claim [84-86] 84, 85, or 86, said polypeptide further comprising a *Helicobacter pylori* CT polypeptide, an immunogenic fragment thereof or an immunogenic derivative thereof, which is immunologically identifiable with the protein expressed by the polynucleotide sequence of SEQ ID NO:2.

91 (Amended). The recombinant polypeptide of claim [84-86] 84, 85, or 86, wherein said polypeptide [further comprising a *Helicobacter pylori* CT polypeptide, an immunogenic fragment thereof or an immunogenic derivative thereof which] contains one or more amino acid substitutions or deletions which do not substantially affect the functional aspects of said antigen.

93 (Amended). The recombinant polypeptide of claim [87] 84, 85, or 86, said polypeptide comprising at least 87 kDa.

94 (Amended) The recombinant polypeptide of claim [87] 84, 85, or 86, said polypeptide comprising at least 100 kDa.

99 (Amended). [The] A recombinant polypeptide of [claim 95] a *Helicobacter pylori* cytotoxin, wherein:

(i) said cytotoxin causes the formation of vacuoles in eukaryotic cells,

(ii) said recombinant polypeptide exhibits substantially no toxicity, or substantially reduced toxicity,

(iii) said recombinant polypeptide can induce the production of antibodies to a *Helicobacter pylori* cytotoxin, and

(iv) said polypeptide is expressed from at least 15 contiguous nucleotides from SEQ ID NO:2.

100 (Amended). The recombinant polypeptide of claim [95] 99, wherein said polypeptide is expressed from at least 30 contiguous nucleotides from SEQ ID NO:2.

101 (Amended). The recombinant polypeptide of claim [95] 99, wherein said polypeptide is expressed from at least 45 contiguous nucleotides from SEQ ID NO:2.